REMARKS

STATUS OF THE CLAIMS

Claims 1, 3-5, and 8-41 are pending in the application. Claims 2 and 6-7 were cancelled. Claims 16-29, 31-36 and 39 were withdrawn pursuant to the restriction requirement. In this amendment, claims 37 and 38 are also withdrawn from further consideration without prejudice, and claims 1, 11 and 30 are amended. In view of the Examiner's decision on the Restriction Requirement, claims 9-29 and 31-40 are withdrawn, and claims 1, 3-5, 8, and 30 are under consideration. New claim 41 has been added. Claim 41 recites "wherein said antibody is unable to cross the bacterial cell membrane." Support for claim 41 is found in paragraph 0007 of the specification as published, US 20070298032. Reconsideration of the instant application is respectfully requested in view of the above amendments and following remarks.

AMENDMENT OF THE SPECIFICATION

The specification has been amended to recite the SEQ ID NOs in paragraphs [0017], [0093] and [0138] (referring to US PG-Pub No. 2007/0298032 of the present application). These SEQ ID NOs were disclosed in the Sequence Listing originally filed; therefore, no new matter is introduced.

AMENDMENT OF THE CLAIMS

Claim 1 has been amended to recite both "an extracellular method of regulating quorum sensing in bacteria" and "antibody to LuxR or a homologue of LuxR prevents said LuxR or homologue of LuxR from being activated by its signalling molecule." The basis for the limitation of the claims to an extracellular method may be found at least on page 3, line 13 of the application as filed. The basis for specifying that the antibody binds to LuxR or a homologue of LuxR may be found in the paragraph bridging pages 4 and 5 of the specification (WO2005/046713). No new matter is introduced. Claims have been amended to conform with United States Patent practice.

Claim 11 has been amended by replacing the sequence "TCNNNKDINQC" with the phrase "of SEQ ID NO: 1", as suggested by the Examiner. No new matter is introduced.

Claim 30 has been amended by correcting the informality. The support is found in the previously presented claims. Therefore, the amendments do not add new matter to the application.

Claims 37 and 38 are withdrawn in this amendment without prejudice to possible rejoinder and/or future prosecution.

THE INVENTION

The instant invention is drawn, in one aspect, to an extracellular method of regulating quorum sensing in bacteria comprising modulating the activation by a signaling molecule of LuxR or a homologue therefore, wherein the binding of an antibody to LuxR or a homologue of LuxR prevents said LuxR or homologue of LuxR from being activated by its signalling molecule.

ARGUMENT

Background to the Invention

The key to the present invention is that until the filing of this application, the scientific community believed that LuxR and its homologues were intracellular proteins. For example, *see* Figure 1 of Hentzer & Givskov (J. Clin. Invest., 2003, 112 (9):1300-1307 – **Exhibit A**) for a review, which was published only 9 days before the priority date of this application.

Indeed, even since the filing of this application, key scientists in the quorum sensing field have published reviews perpetuating this belief that LuxR and its homologues are intracellular. For example, Winans (ACS Chemical Biology, 2006, 1:429-431 – **Exhibit B**) shows that LuxR is intracellular in the diagram on page 430. The signaling molecule is shown to move in and out of the cell while LuxR is shown to remain inside the cell and separated from the inner and outer cell membrane. In addition, Waters and Bassler (Ann. Rev. Cell & Dev. Biol. 2005, 21:319-346 – **Exhibit C**) also show LuxR to be intracellular, with the signaling molecule freely diffusing in and out of the cell (see Figure 1, page 321). A similar scenario is shown in Figure 5 on page 328 for the LuxR homologues LasR and RhIR, with these proteins shown to be intracellular while their respective autoinducers diffuse in and out of the cell.

Thus, the common understanding before the filing of this application was that LuxR and its homologues are intracellular and are not displayed on the cell surface. As such, the protein could not be displayed to and interact with antibody.

It must also be remembered that antibodies are large proteins. The antibodies in the polyclonal antisera used in the application have an approximate mass of 152 kDa. Such a protein is far too large to simply diffuse through the bacterial membranes. Furthermore, Applicants are not aware of any precedents for a protein transporter (or other mechanism) that would allow the transfer of such a large protein through the outer and inner bacterial membranes and across the periplasmic space.

Therefore, in the absence of any teaching in the prior art of either LuxR or its homologues being presented on the cell surface, or of antibodies being able to enter the bacterial cell, a person of ordinary skill in the relevant art would not have believed that they could interact due to the cell membrane acting as a barrier. Based on the common understanding, there was no way that LuxR or its homologues could interact with antibody, other than by lysing (and therefore killing) the bacterial cell.

The Present Invention

The present invention as set forth in the claims currently pending relate to:

> "1. *An extracellular method of regulating quorum sensing in bacteria comprising modulating the activation by a signaling molecule of LuxR or a homologue therefore, wherein the binding of an antibody to LuxR or a homologue of LuxR prevents said LuxR or homologue of LuxR from being activated by its signalling molecule."*

The present application shows, contrary to popular belief, that LuxR and its homologues are not intracellular proteins. On the contrary, these proteins are found on the outer surface of the bacterial membrane. This teaching is contrary to popular belief both before and after the filing date of the application, which indicates the inventive nature of the claims.

As explained above, the skilled person would have dismissed the idea of using antibodies against LuxR or homologues thereof in an attempt to modulate quorum sensing as they would

have believed that (a) these molecules were intracellular, and (b) antibodies are too large to pass through the inner and outer bacterial membranes. Therefore, there would have been no antibody-antigen interaction.

Restriction Requirement

The Examiner has made the Restriction Requirement final in spite of the Applicants' election with traverse submitted in the last response. Applicants reserve the right to petition on the propriety of this decision.

Objection to Claim 38

The Examiner objected to claim 38 for being a "use" claim and an improper multiple dependant claim. Claim 38 has been withdrawn from further consideration, thus rendering this objection moot.

Objection to the Drawings

The Examiner objected to the drawings allegedly because the SEQ ID NOs of the sequences listed in Figure 1 are not recited in the Brief Description of the Drawings. In response, Applicants have amended the specification by incorporating the SEQ ID NOs (i.e., SEQ ID NO: 2 to SEQ ID NO: 16) of the sequences listed in Figure 1 into the Brief Description of the Drawings, namely, paragraph [0093] of US PG-Pub No. 2007/0298032 (corresponding to page 18, first paragraph as originally filed). Thus, this objection has been overcome.

Rejection of Claim 30 Based on 35 U.S.C. § 101

The Examiner rejected claim 30 under 35 U.S.C. § 101 as being indefinite allegedly because it merely recites a "use" without any active positive steps delimiting how this use is actually practiced. Claim 30 has been amended by changing the "use" claim to a method claim depending from claim 1 or 3. Therefore, this rejection has been overcome.

Rejection of the Claims Based on 35 U.S.C. § 102(b)

The Examiner rejected claims 1, 3-5, 8, 30, and 37 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. PG-Pub No. 2003/0095985 to Kende *et al.* (the "Kende *et al.*"). Applicants respectfully traverse. Kende *et al.* relates to an immunogenic conjugate comprising a

carrier molecule coupled to an autoinducer of a Gram negative bacteria. Kende *et al.* suggests use of the conjugate as a vaccine or to raise antibodies to the autoinducer for use in therapy.

The autoinducer corresponds to the signaling molecule of LuxR (*i.e.*, not LuxR irself) of the present application. In contrast, the focus of the present application is use of an antibody to LuxR or a homologue of LuxR which prevents the LuxR or homologue of LuxR from being activated by its signaling molecule. Kende *et al.* contains no disclosure or suggestion of use of an antibody to LuxR or homologue of LuxR.

Therefore, for at least these reasons, Applicants respectfully request the Examiner to withdraw this ground of rejection.

Rejection of the Claims Based on 35 U.S.C. § 102(e)

The Examiner rejected claims 1, 3, 5, 8, 30, and 37 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. PG-Pub 2004/0171020 to Ulrich *et al.* (the "Ulrich *et al.*"). Applicants respectfully traverse. The disclosures of Ulrich *et al.* are based on and entirely consistent with the erroneous belief held in the art at the filing date of the present invention that LuxR and its homologues were intracellular proteins.

In particular, Ulrich *et al.* contains no disclosure or suggestion that LuxR may be found on the outer surface of the bacterial membrane. For example, in paragraph [0006] it is noted that "*AHLs are secreted into the extracellular medium and diffused back into the cell when a high concentration has been reached*". AHLs refer to N-acyl-homoserine lactones, which are the small signaling molecules which bind to LuxR and activate or repress gene expression. Thus, Ulrich *et al.* reinforces the erroneous belief that the signaling molecules (AHLs) must diffuse into the cell in order to bind to LuxR intracellularly.

In paragraphs [0021] to [0027], Ulrich *et al.* suggests preparation of antibodies to AHS transcriptional regulator (*i.e.*, LuxR). However, the suggestion to provide such antibodies is in the context of detection of AHS transcriptional regulators (LuxR) and not in the context of regulation of quorum sensing.

Similarly, paragraph [0071] of Ulrich *et al.* refers to the preparation of antibodies but does not refer to their use, and paragraphs [0078] and [0080] further expand on the use of antibodies to AHS transcriptional regulator (LuxR) in the detection and assay of AHS

transcriptional regulator, further reinforcing the fact that disclosure of antibodies to LuxR is in the context of detection and assay and not modulation of LuxR.

Paragraph [0093] of Ulrich *et al.* refers to antibodies or compounds capable of reducing or inhibiting the synthase or synthase transcriptional regulator. However, Ulrich *et al.* contains no disclosure or suggestion that LuxR might be found on the outer surface of the bacterial membrane. Accordingly, there is no teaching or suggestion that antibodies to LuxR might be used in an extracellular method or regulating quorum sensing in bacteria as presently claimed. Indeed, reference in paragraph [0093] of Ulrich *et al.* to providing antibodies "*as part of an expression vector capable of being expressed in the target cell such that the synthase-reducing of inhibiting agent is produced*" clearly indicates that an intracellular mechanism is envisaged, and not an extracellular process as presently claimed.

Therefore, for at least these reasons, it is believed that the present invention is both novel and inventive over the cited prior art and that the claims as amended are in order for allowance. Applicants respectfully request the Examiner to withdraw this ground of rejection.

Sequence Requirements

The Examiner objected to the specification and claim 11 allegedly because of lack of proper recitation of the SEQ ID NOs for the amino acid sequences of 4 or more residues disclosed or claimed. In response, Applicants have amended claim 11 by replacing the sequence with the phrase "of SEQ ID NO: 1" and amended the specification, specifically in US PG-Pub No. 2007/0298032, paragraph [0017] (corresponding to page 5, paragraph 3 as originally filed) and paragraph [0138] (corresponding to page 24, last paragraph), by reciting the phrase "SEQ ID NO: 1" at appropriate places. The support is found in the specification and the Sequence Listing originally filed. Therefore, this deficiency has been overcome.

CONCLUSION

In view of the foregoing, Applicants believe all the issues raised by the Examiner have been fully addressed and all the pending claims in this application are in a condition for allowance, and an early notice to this effect is earnestly solicited

To the extent that any extra fees are required, in connection with receipt, acceptance and/or consideration of this paper and/or any accompanying papers submitted herewith, please charge all such fees to Deposit Account 50-1943.

Should Examiner have any questions or comments with respect to this response, it is respectfully requested that the Examiner telephone Applicants' attorney at (609) 844-3020 to discuss any additional matters.

Respectfully submitted,

Date: April 28, 2010

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